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Single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews (Review)

Moore RA, Derry S, Aldington D, Wiffen PJ

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TABLE OF CONTENTS

[Overview of Reviews]

Single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews

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ABSTRACT

Background

This is an updated version of the original Cochrane overview published in Issue 9, 2011. That overview considered both efficacy and adverse events, but adverse events are now dealt with in a separate overview.

Thirty-nine Cochrane reviews of randomised trials have examined the analgesic efficacy of individual drug interventions in acute postoperative pain. This overview brings together the results of those individual reviews and assesses the reliability of available data.

Objectives

To summarise the efficacy of pharmaceutical interventions for acute pain in adults with at least moderate pain following surgery who have been given a single dose of oral analgesic.

Methods

We identified systematic reviews in *the Cochrane Database of Systematic Reviews* in *The Cochrane Library* through a simple search strategy. All reviews were overseen by a single review group, had a standard title, and had as their primary outcome the number of participants with at least 50% pain relief over four to six hours compared with placebo. For individual reviews, we extracted the number needed to treat for an additional beneficial outcome (NNT) for this outcome for each drug/dose combination, and also the percentage of participants achieving at least 50% maximum pain relief, the mean of mean or median time to remedication, and the percentage of participants remedicating by six, eight, 12, or 24 hours. Where there was adequate information for pairs of drug and dose (at least 200 participants, in at least two studies), we defined the addition of four comparisons of typical size (400 participants in total) with zero effect as making the result potentially subject to publication bias and therefore unreliable.

Main results

The overview included 39 separate Cochrane Reviews with 41 analyses of single dose oral analgesics tested in acute postoperative pain models, with results from about 50,000 participants in approximately 460 individual studies. The individual reviews included only high-quality trials of standardised design, methods, and efficacy outcome reporting. No statistical comparison was undertaken.

Reliable results (high quality information) were obtained for 53 pairs of drug and dose in painful postsurgical conditions; these included various fixed dose combinations, and fast acting formulations of some analgesics. NNTs varied from about 1.5 to 20 for at least 50% maximum pain relief over four to six hours compared with placebo. The proportion of participants achieving this level of benefit varied from about 30% to over 70%, and the time to remedication varied from two hours (placebo) to over 20 hours. Good (low) NNTs were obtained with ibuprofen 200 mg plus paracetamol (acetaminophen) 500 mg (NNT compared with placebo 1.6; 95% confidence interval 1.5 to 1.8), ibuprofen fast acting 200 mg (2.1; 1.9 to 2.3); ibuprofen 200 mg plus caffeine 100 mg (2.1; 1.9 to 3.1), diclofenac potassium 50 mg (2.1; 1.9 to

2.5), and etoricoxib 120 mg (1.8; 1.7 to 2.0). For comparison, ibuprofen acid 400 mg had an NNT of 2.5 (2.4 to 2.6). Not all participants had good pain relief and, for many pairs of drug and dose, 50% or more did not achieve at least 50% maximum pain relief over four to six hours.

Long duration of action (eight hours or greater) was found for etoricoxib 120 mg, diflunisal 500 mg, paracetamol 650 mg plus oxycodone 10 mg, naproxen 500/550 mg, celecoxib 400 mg, and ibuprofen 400 mg plus paracetamol 1000 mg.

There was no evidence of analgesic effect for aceclofenac 150 mg, aspirin 500 mg, and oxycodone 5 mg (low quality evidence). No trial data were available in reviews of acemetacin, meloxicam, nabumetone, nefopam, sulindac, tenoxicam, and tiaprofenic acid. Inadequate amounts of data were available for nine drugs and doses, and data potentially susceptible to publication bias for 13 drugs and doses (very low quality evidence).

Authors' conclusions

There is a wealth of reliable evidence on the analgesic efficacy of single dose oral analgesics. Fast acting formulations and fixed dose combinations of analgesics can produce good and often long-lasting analgesia at relatively low doses. There is also important information on drugs for which there are no data, inadequate data, or where results are unreliable due to susceptibility to publication bias. This should inform choices by professionals and consumers.

PLAIN LANGUAGE SUMMARY

Comparing single doses of oral analgesics for acute pain in adults after operation

Acute pain is often felt soon after injury. Most people who have surgery have moderate or severe pain afterwards. Painkillers (analgesics) are tested in people with pain, often following the removal of wisdom teeth. In all these studies the participants have to have at least moderate pain in order for there to be a sensitive measure of pain-relieving properties. The pain is usually treated with painkillers taken by mouth. Results can be applied to other forms of acute pain.

In May 2015 we performed searches to update an overview review originally published in 2011. *The Cochrane Library* now has 39 reviews of oral analgesic medicines, with 41 different medicines at various doses. These involved about 50,000 participants in about 450 studies. This overview sought to bring all the high quality information together about how well the medicines work; side effects are reported in a different overview.

For some medicines there were no published trials. For other medicines there was inadequate information. For some medicines, there was adequate information, but the results could be overturned by just a few unpublished studies in which there was no effect. None of these could be regarded as reliable. There remained 53 pairs of medicine and dose with reliable evidence.

The range of results with single dose analgesics in participants with moderate or severe acute pain was from 7 out of 10 (70%) achieving good pain relief with the best medicine to about 3 out of 10 (30%) with the worst medicine. No medicine produced high levels of pain relief in all participants.

The period over which pain was relieved also varied, from about two hours to about 20 hours. Good results were found for medicines combined in a fixed dose in a single tablet, or medicines made for rapid absorption from the stomach.

Commonly used analgesic medicines at the recommended or licensed doses produce good pain relief in many, but not all, people with acute pain. The reasons for this are varied, but people in pain should not be surprised if medicines they are given do not work for them. Alternative analgesic medicines or methods should be found that do work.

BACKGROUND

This overview is an update of an overview 'Single dose oral analgesics for acute postoperative pain in adults', originally published in Issue 9, 2011 (Moore 2011a), and is concerned with efficacy; a separate review now covers adverse events (Moore 2015d).

Description of the condition

Acute pain occurs as a result of tissue damage either accidentally due to an injury or as a result of surgery. Acute postoperative (after surgery) pain is a manifestation of inflammation due to tissue injury. The management of postoperative pain and inflammation is a critical component of patient care and is important for cost-effective use of healthcare resources. Good postoperative pain management helps to achieve a satisfied patient who is in hospital or at home and unable to carry out normal activities for a minimal amount of time.

Description of the interventions

Analgesics used for relief of postoperative pain include so called 'mild' or step 1 (WHO 2010) analgesics, such as paracetamol (acetaminophen), and nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and celecoxib, 'moderate' or step 2 analgesics, which are weaker opioids such as codeine, and 'strong' or step 3 analgesics, which are strong opioids such as oxycodone and fentanyl.

Paracetamol has become one of the most used antipyretic and analgesic drugs worldwide, and is often also used in combination with other stronger analgesics. NSAIDs as a class are the most commonly prescribed analgesic medications worldwide and their efficacy for treating acute pain has been well demonstrated (Moore 2003). Opioids as a class have long been used to treat pain during and immediately after surgery, because they can be given parenterally, and because dose can be titrated to effect for immediate pain relief. Oral opioids are less often used alone, but are used in fixed-dose combination with drugs such as paracetamol or ibuprofen (McQuay 1997).

This overview considered only oral administration of analgesics. Parenteral administration by intravenous, intramuscular, or subcutaneous injections is useful for some drugs immediately following surgery, particularly for people unable to swallow or where oral intake is not possible for other reasons (McQuay 1997). Most postoperative patients can swallow and oral administration is clearly the least technically demanding and cheapest method of drug delivery, especially when the benefits of injection over oral administration have not been demonstrated, as with NSAIDs (Tramer 1998).

Acute pain trials

Postoperative pain relief is part of a package of care that covers the preoperative (before surgery), intraoperative (during surgery), and postoperative periods and involves using the best evidence at all times (Kehlet 1998). This overview involves only one aspect of one part of the patient journey, namely how well different oral drug interventions work to relieve pain after surgery. The choice of a particular oral drug intervention depends on the clinical and operational circumstances and how any choice fits in with local care pathways. This overview only examined the efficacy of oral drugs: how to use them effectively in the relief of postoperative pain is a question not addressed here.

Clinical trials measuring the efficacy of analgesics in acute pain have been standardised over many years. To show that the analgesic is working, it is necessary to use a placebo (McQuay 2005; McQuay 2006). There are clear ethical considerations in doing this. These ethical considerations are answered by using acute pain situations where the pain is expected to go away, and by providing additional analgesia, commonly called rescue analgesia, if the pain has not diminished after about an hour. This is reasonable, because not all participants given an analgesic will have acceptable pain relief. Approximately 18% of participants given placebo will have adequate pain relief (Moore 2006), and up to 50% may have inadequate analgesia with active medicines. The use of additional or rescue analgesia is therefore important for all participants in the trials.

Trials have to be randomised and double-blind. Typically, in the first few hours or days after an operation, participants develop pain that is moderate to severe in intensity, and will then be given the test analgesic or placebo. Pain is measured using standard pain intensity scales immediately before the intervention, and then using pain intensity and pain relief scales over the following four to six hours for shorter acting drugs, and up to 12 or 24 hours for longer acting drugs. Half the maximum possible pain relief or better over the specified time period (at least 50% pain relief) is typically regarded as a clinically useful outcome across various different pain conditions (Moore 2013). For people given rescue medication, it is usual for no additional pain measurements to be made, and for all subsequent measures to be recorded as initial pain intensity or baseline (zero) pain relief (baseline observation carried forward). This process ensures that analgesia from the rescue medication is not wrongly ascribed to the test intervention. In some trials the last observation is carried forward, which gives an inflated response for the test intervention compared with placebo, but the effect has been shown to be negligible over four to six hours (Moore 2005). People usually remain in the hospital or clinic for at least the first six hours following the intervention, with measurements supervised, although they may then be allowed home to make their own measurements in trials of longer duration.

Important characteristics of analgesic efficacy include the proportion of participants who experience clinically useful levels of pain relief at a given dose, the duration of useful pain relief (which informs dosing intervals), and the drug's tolerability. Single dose studies can provide us with information on the number needed to treat for an additional beneficial outcome (NNT) for at least 50% maximum pain relief over four to six hours compared with placebo and the proportions of participants achieving that outcome, the number needed to treat to prevent (NNTp) use of rescue medication and the proportions needing rescue medication, and the median (or mean) time to use of rescue medication.

How the intervention might work

Nonsteroidal anti-inflammatory drugs

NSAIDs reversibly inhibit the enzyme cyclooxygenase (prostaglandin endoperoxide synthase or COX), now recognised to consist of two isoforms, COX-1 and COX-2, mediating production of prostaglandins and thromboxane A2 (FitzGerald 2001). Prostaglandins mediate a variety of physiological functions

such as maintenance of the gastric mucosal barrier, regulation of renal blood flow, and regulation of endothelial tone. They also play an important role in inflammatory and nociceptive (pain) processes. However, relatively little is known about the mechanism of action of this class of compounds aside from their ability to inhibit cyclooxygenase-dependent prostanoid formation (Hawkey 1999). Aspirin is a special case, in that it irreversibly blocks COX-1.

Formulation of NSAID may be important for driving early and overall good pain relief, as seen with paracetamol, and diclofenac (Diclofenac 2015; Moore 2014; Moore 2015a).

Paracetamol

Paracetamol lacks significant anti-inflammatory activity, implying a mode of action distinct from that of NSAIDs. Despite years of use and research, however, the mechanisms of action of paracetamol are not fully understood. Paracetamol has previously been shown to have no significant effects on COX-1 or COX-2 (Schwab 2003), but has been considered as a selective COX-2 inhibitor (Hinz 2008). Significant paracetamol-induced inhibition of prostaglandin production has been demonstrated in tissues in the brain, spleen, and lung (Botting 2000; Flower 1972). A 'COX-3 hypothesis' wherein the efficacy of paracetamol is attributed to its specific inhibition of a third cyclooxygenase isoform enzyme, COX-3 (Botting 2000; Chandrasekharan 2002; PIC 2008), now has little credibility and a central mode action of paracetamol is thought to be likely (Graham 2005).

Opioids

Opioids bind to specific receptors in the central nervous system (CNS), causing reduced pain perception and reaction to pain, and increased pain tolerance. In addition to these desirable analgesic effects, binding to receptors in the CNS may cause adverse events such as drowsiness and respiratory depression, and binding to receptors elsewhere in the body (primarily the gastrointestinal tract) commonly causes nausea, vomiting, and constipation. In an effort to reduce the amount of opioid required for pain relief, and so reduce problematic adverse events, opioids are commonly combined with non-opioid analgesics, such as paracetamol (Pasternak 2012).

Why it is important to do this overview

Knowing the relative efficacy of different analgesic drugs at various doses, under standard conditions, can be helpful. Choice of drug for an individual patient will depend on relative efficacy and a number of other factors including availability, cost, tolerability, and individual considerations, such as the person's history and contraindications to a particular medication, and their ability to remedicate orally. A large number of systematic reviews of individual oral analgesics versus placebo in acute postoperative pain have been completed, using identical methods. An overview is required to facilitate indirect comparisons between individual analgesics, providing estimates of relative efficacy that can help to inform treatment choices.

OBJECTIVES

To summarise the efficacy of pharmaceutical interventions for acute pain in adults with at least moderate pain following surgery who have been given a single dose of oral analgesic.

METHODS

Criteria for considering reviews for inclusion

All Cochrane reviews of randomised controlled trials (RCTs) of single dose oral analgesics for acute postoperative pain in adults (aged 15 years or greater).

Search methods for identification of reviews

We searched the*Cochrane Database of Systematic Reviews* (Issue 5 of 12, 2015) in *The Cochrane Library* for relevant reviews. See Appendix 1 for the search strategy. A series of Cochrane reviews have been conducted by the same team, covering analgesics identified in the British National Formulary.

Data collection and analysis

Two review authors (RAM, SD) independently carried out searches, selected reviews for inclusion, carried out assessment of methodological quality, and extracted data. We resolved any disagreements by discussion, involving a third review author if necessary.

Selection of reviews

Included reviews assessed RCTs evaluating the effects of a single oral dose of analgesic given for relief of moderate to severe postoperative pain in adults, compared with placebo, and included:

- a clearly defined clinical question;
- details of inclusion and exclusion criteria;
- details of databases searched and relevant search strategies;
- participant-reported pain relief; and
- summary results for at least one desired outcome.

Data extraction and management

We extracted data from the included reviews using a standard data extraction form. We used original study reports only if specific data were missing.

We collected information on the following:

- number of included studies and participants;
- drug, dose, and formulation; fast acting formulations were of great interest since, for ibuprofen, individual participant level analysis and other analyses have demonstrated that speed of absorption is important in generating good overall pain relief, and also long duration pain relief (Moore 2014; Moore 2015a). The effects of taking analgesics with food can profoundly affect the pharmacokinetics of drug absorption (Moore 2015b), but this was not an issue here as studies were universally carried out on fasting participants, as best it is possible to judge;
- pain model (dental, other surgical).

We sought risk ratio (RR) and numbers needed to treat to benefit (NNT) or calculated these for analgesic versus placebo the following efficacy outcomes:

- participants with 50% or greater maximum pain relief over four to six hours (participant-reported): this outcome encapsulates both degree of pain relief and duration of the effect, and was a dichotomous measure of success over a defined period following drug ingestion;

- participants using rescue medication (or mean or median if appropriate, for example for time to remedication).

We extracted or calculated 95% confidence intervals (CIs) for all RRs and NNTs. NNTs were not calculated when the 95% CIs of the RR included 1.

We also sought information on the proportions of individuals with the outcomes listed above, and median or mean time to use of rescue medication. Adverse event information was collected, but is the subject of a different review (Moore 2015d).

Assessment of methodological quality of included reviews

Quality of included reviews

All included reviews were carried out according to a standard protocol that satisfied the criteria specified in the 'assessment of multiple systematic reviews' (AMSTAR) measurement tool (Shea 2007) for rigorous methodological quality.

Each review was required to:

- provide an a priori design;
- carry out duplicate study selection and data extraction;
- carry out a comprehensive literature search;
- include published and unpublished studies irrespective of language of publication;
- provide a list of studies (included and excluded);
- assess and document the scientific quality of the included studies;
- use the scientific quality of the included studies appropriately in formulating conclusions;
- use appropriate methods to combine the findings of studies; and
- state conflicts of interests.

For each review we assessed the likelihood of publication bias by calculating the number of participants in studies with zero effect (relative benefit of one) that would be needed to give an NNT too high to be clinically relevant (Moore 2008). In this case we considered an NNT of ≥ 10 for the outcome 'at least 50% maximum pain relief over four to six hours' to be the cut-off for clinical relevance. We used this method because statistical tests for presence of publication bias have been shown to be unhelpful (Thornton 2000).

Quality of evidence in included reviews

All included reviews used only primary studies that were both randomised and double-blind, so minimising the risk of bias from these items. All used participants with at least moderate pain intensity at baseline, providing a sensitive assay of analgesic efficacy. All used standard methods and reported standard outcomes, or provided data from which they could be calculated using validated methods. For studies in acute pain lasting up to six hours, it has been shown that use of last observation carried forward rather than baseline observation carried forward does not significantly influence results (Moore 2005).

We used the amount and quality of evidence to report results in a hierarchical way. We did this to try to conform to GRADE descriptors of evidence. In this overview, issues of evidence quality were not an issue, as all included reviews were likely to fulfil minimum criteria and eliminate most sources of bias. The main issue remaining was of the amount of information available and potential susceptibility to publication bias. We therefore split the available information into five groups, and gave them GRADE descriptors.

- Drugs and doses for which Cochrane reviews found no information (very low quality evidence).
- Drugs and doses for which Cochrane reviews found inadequate information: fewer than 200 participants in comparisons, in at least two studies (very low quality evidence) (Moore 1998).
- Drugs and doses for which Cochrane reviews found no evidence of effect or evidence of no effect: more than 200 participants in comparisons, but where there was no statistically significant difference from placebo (descriptor depends on individual result).
- Drugs and doses for which Cochrane reviews found evidence of effect, but where results were potentially subject to publication bias. We considered the number of additional participants needed in studies with zero effect (relative benefit of one) required to change the NNT for at least 50% maximum pain relief to an unacceptably high level (in this case the arbitrary NNT of 10) (Moore 2008). Where this number was less than 400 (equivalent to four studies with 100 participants per comparison, or 50 participants per group), we considered the results to be susceptible to publication bias and therefore unreliable (low quality evidence).
- Drugs and doses for which Cochrane reviews found evidence of effect, where results were reliable and not subject to potential publication bias (high quality evidence).

Data synthesis

We used information on the selected efficacy outcomes to draw up comparisons of analgesic efficacy, using indirect comparison of different drugs from almost identical clinical trial conditions, with placebo as a common comparator (Glenny 2005; Song 2003). The trials used in these reviews have a high level of clinical and methodological homogeneity, having used consistent validated methods for more than 50 years to measure pain intensity and pain relief in participants with established baseline pain of at least moderate severity, over at least four to six hours, and with placebo as a common comparator. Some of these data have been used to demonstrate the superiority of indirect over direct comparison in circumstances where there are large amounts of indirect data and small amounts of direct data (Song 2003).

The case mix (principally dental versus other surgery) has previously been shown to have minimal effect on some descriptors, such as NNT (Barden 2004). The bulk of the results derive from studies of pain following third molar extraction, and in this updated review we chose not to separate results for dental versus other types of surgery. The previous version of this review had not shown any significant systematic differences, and so a potentially complicating factor has been removed in this update.

Comparative efficacy results are expressed as:

- participants achieving at least 50% maximum pain relief, as a percentage and as an NNT, compared with placebo;
- duration of analgesia, as mean or median duration, and percentage of participants remedicating by various times after dosing.

RESULTS

The overview included 39 separate Cochrane reviews investigating 41 analgesics or analgesic combinations given as single oral doses in acute postoperative pain conditions (Aceclofenac 2009; Acemetacin 2009; Aspirin 2012; Celecoxib 2013; Codeine 2010; Dexibuprofen 2009; Diclofenac 2015; Diflunisal 2010; Dihydrocodeine 2000; Dipyrone 2010; Etodolac 2009; Etoricoxib 2014; Fenbufen 2009; Fenoprofen 2011; Flurbiprofen 2009; Gabapentin 2010; Ibuprofen 2009; Ibuprofen + caffeine 2015; Ibuprofen + codeine 2015; Ibuprofen + oxycodone 2013; Ibuprofen + paracetamol 2013; Indometacin 2004; Ketoprofen and dexketoprofen 2009; Lornoxicam 2009; Lumiracoxib 2010; Mefenamic acid 2011; Meloxicam 2009; Nabumetone 2009; Naproxen 2009; Nefopam 2009; Paracetamol 2008; Paracetamol + codeine 2009; Paracetamol ± dextropropoxyphene 1999; Paracetamol ± oxycodone 2009; Piroxicam 2000; Rofecoxib 2009; Sulindac 2009; Tenoxicam 2009; Tiaprofenic acid 2009).

In total, there were 467 studies, combining the number of studies in the individual reviews. However, many studies had both placebo and active comparators; for example, ibuprofen was used as an active comparator in many of them. The number of unique studies was probably closer to 450.

All of the reviews used the same methodological approach and the same primary outcome of NNT for at least 50% maximum pain relief over four to six hours compared with placebo. The sum of the number of participants in the reviews was 58,017, but there will have been double-counting of placebo participants both within reviews (comparison of different drug doses separately against placebo) and between reviews (drugs such as ibuprofen are commonly used as an active comparator for new test analgesics and placebo arms will be counted in reviews of both analgesics). In these circumstances the number of unique participants is more likely to be of the order of 50,000.

Description of included reviews

Included reviews each had the same structure and organisation, and used identical methods based on criteria established by extensive analysis and validation, using individual participant data (see Table 1). They all used the same criteria and typically these were as follows.

- Adults with established pain of at least moderate intensity (Collins 1997).
- Single dose oral administration of analgesic or placebo (with additional analgesia available, typically after 60 to 120 minutes).
- Randomised, double-blind studies.
- Pain assessed by participants using standard pain intensity and pain relief scales.
- Study duration of four hours or more.
- Searching included electronic searches, plus databases created by handsearching the older literature, now part of the Cochrane Central Register of Controlled Trials (CENTRAL). Searching also included different retail names for drugs.
- No language restriction on included papers.
- Assessment of study quality according to established criteria and minimum criteria for inclusion.

Methodological quality of included reviews

All the reviews:

- had an a priori design;
- performed duplicate study selection and data extraction;
- had a comprehensive literature search;
- used published and any unpublished studies included irrespective of language of publication, although not all reviews contacted companies or researchers for unpublished trial data;
- provided a list of included and excluded studies;
- provided characteristics of included studies;
- assessed and documented the scientific quality of the included studies;
- the scientific quality of the included studies was used appropriately in formulating conclusions, because only studies with minimal risk of bias were included (a particular issue was trial size, but conclusions were not drawn from inadequate data sets, based on previously established criteria (Moore 1998));
- used appropriate methods to combine findings of studies and, importantly, provided analyses according to drug dose; and
- conflict of interest statements were universal.

The reviews all used validated methods for conversion of mean to dichotomous data (Moore 1996; Moore 1997a; Moore 1997b), providing the number and proportion of participants with the clinically relevant outcome of at least 50% maximum pain relief. Remedication is common within a few hours, particularly with placebo, therefore the method of imputing data after remedication (withdrawal) is potentially of importance to the measurement of treatment effect. In the case of the primary outcome of the reviews, that of NNT for at least 50% maximum pain relief compared with placebo over four to six hours, the imputation method had been shown not to make any appreciable difference (Moore 2005), though use of last observation carried forward tended to overestimate treatment effect compared with baseline observation carried forward over longer periods (Moore 2005).

Effect of interventions

To assess the effects of interventions, we used a five-step process.

- Note drugs for which no acute pain data could be found.
- Note pairs of drug and dose with inadequate amounts of information, where inadequate was defined as fewer than two studies and 200 participants - with limited flexibility around 200 participant limit).
- Note pairs of drug and dose with data but no evidence of effect, or with evidence of no effect.
- Note pairs of drug and dose with high susceptibility to publication bias, as defined in the 'Methods' section.
- Note pairs of drug and dose for which Cochrane reviews found evidence of effect, where results were reliable (backed by high quality data not subject to methodological bias, of sufficient size for random chance effects to be unimportant) and not subject to potential publication bias (high quality evidence). For this group we reported several efficacy outcomes.

Table 1 shows all extracted information from all reviews

1. Drugs for which Cochrane reviews found no information

We found no clinical trial information for seven drugs (Acemetacin 2009; Meloxicam 2009; Nabumetone 2009; Nefopam 2009; Sulindac 2009; Tenoxicam 2009; Tiaprofenic acid 2009) (very low quality evidence).

2. Drugs for which Cochrane reviews found inadequate information (fewer than 200 participants in comparisons in two studies)

We found only limited information (very low quality evidence) for 10 drugs at various doses.

- Aceclofenac 150 mg (137 participants in one study) (Aceclofenac 2009).
- Dexibuprofen 200 mg and 400 mg (176 participants with the two doses in one study) (Dexibuprofen 2009).
- Dextropropoxyphene 130 mg (50 participants in one study) (Paracetamol ± dextropropoxyphene 1999).
- Diclofenac fast-acting 100 mg (168 participants in two studies) (Diclofenac 2015).
- Diflunisal 125 mg (120 participants in two studies) (Diflunisal 2010).
- Etoricoxib 60 mg (124 participants in one study) (Etoricoxib 2014).
- Fenbufen 400 and 800 mg (46 participants with the two doses in one study) (Fenbufen 2009).
- Ibuprofen 800 mg (76 participants in one study) (Ibuprofen 2009).
- Indometacin 50 mg (94 participants in one study) (Indometacin 2004).
- Lornoxicam 4 mg (151 participants in two studies) (Lornoxicam 2009).

3. Drugs for which Cochrane reviews found no evidence of effect or evidence of no effect

There was evidence for lack of effect for two pairs of drug and dose, with no difference between active drug and placebo.

- Aspirin 500 mg (213 participants in two studies; RR 1.3; 95% CI 0.8 to 2.0) (Aspirin 2012).
- Oxycodone 5 mg (317 participants in three studies; RR 1.1; 95% CI 0.8 to 1.6) (Paracetamol ± oxycodone 2009).

We classified this as low quality evidence because of the limited numbers of participants.

4. Pairs of drug and dose for which Cochrane reviews found evidence of effect, but where results were potentially subject to publication bias

Summary table A shows the pairs of drug and dose where our judgement was of high susceptibility to publication bias (low quality evidence). The number in the susceptibility to publication bias column refers to the number of participants in studies with null effect needed to produce an NNT worse than 10.

These tended to have larger (less effective) NNTs, or small numbers of participants, or both. The appropriateness or otherwise of this categorisation is discussed below, but these results are the least reliable of those available from the reviews. For gabapentin, the NNT was above 10, and based on a relatively small number of participants.

Summary table A: Results potentially subject to publication bias

Drug	Dose (mg)	Number of		At least 50% maximum pain relief over 4 - 6 hours						Susceptibility to publication bias
				Number with outcome/total		Percent with outcome		Risk ratio (95% CI)	NNT (95% CI)	
		Studies	Participants	Active	Placebo	Active	Placebo			
Dextropropoxyphene	65	6	440	85/214	60/226	40	27	1.5 (1.2 to 1.9)	7.7 (4.6 to 22)	131
Diflunisal	250	3	195	49/98	16/97	47	16	2.9 (1.8 to 4.6)	3.3 (2.3 to 5.5)	396
Diclofenac fast-acting	25	2	325	36/165	4/160	22	3	8.7 (3.2 to 24)	5.2 (3.8 to 8.0)	325
Diclofenac sodium	50	2	313	58/193	18/120	30	15	2.0 (1.3 to 3.3)	6.6 (4.1 to 17)	161
Dihydrocodeine	30	3	194	31/97	19/97	32	20	1.6 (1.01 to 2.5)	8.1 (4.1 to 540)	46
Etodolac	50	4	360	44/154	34/206	29	17	1.7 (1.1 to 2.6)	8.3 (4.8 to 30)	74
Gabapentin	250	3	327	26/177	8/150	15	5	2.5 (1.2 to 5.0)	11 (6.4 to 35)	NNT above 10
Ibuprofen	50	3	316	50/159	16/157	31	10	3.2 (1.9 to 5.1)	4.7 (3.3 to 8.0)	356
Mefenamic acid	500	2	256	60/126	29/130	48	22	2.1 (1.5 to 3.1)	4.0 (2.7 to 7.1)	384
Naproxen	200/220	2	202	54/120	13/82	45	16	2.9 (1.6 to 5.1)	3.4 (2.4 to 5.8)	392
Oxycodone	15	3	228	61/113	37/115	54	32	1.7 (1.2 to 2.3)	4.6 (2.9 to 11)	268
Paracetamol + codeine	300+30	6	690	123/379	56/311	32	18	1.9 (1.4 to 2.5)	6.9 (4.8 to 12)	310
Paracetamol + oxycodone	325+5	3	388	60/221	14/167	27	8	3.6 (2.1 to 6.3)	5.4 (3.9 to 8.8)	331

5. Pairs of drug and dose for which Cochrane reviews found evidence of effect, where results were reliable and not subject to potential publication bias

Reliable results are presented alphabetically in Summary table B; about 45,000 participants contributed data to these analyses. Figure 1 shows the NNT compared with placebo for at least 50% maximum pain relief over four to six hours for all types of surgery by rank order of the NNT. For codeine 60 mg, although the NNT was above 10, it was based on over 2400 participants and we deemed that a reliable result (high quality evidence).

Figure 1. Single dose oral analgesics in moderate or severe pain: NNT for at least 50% maximum pain relief over four to six hours.

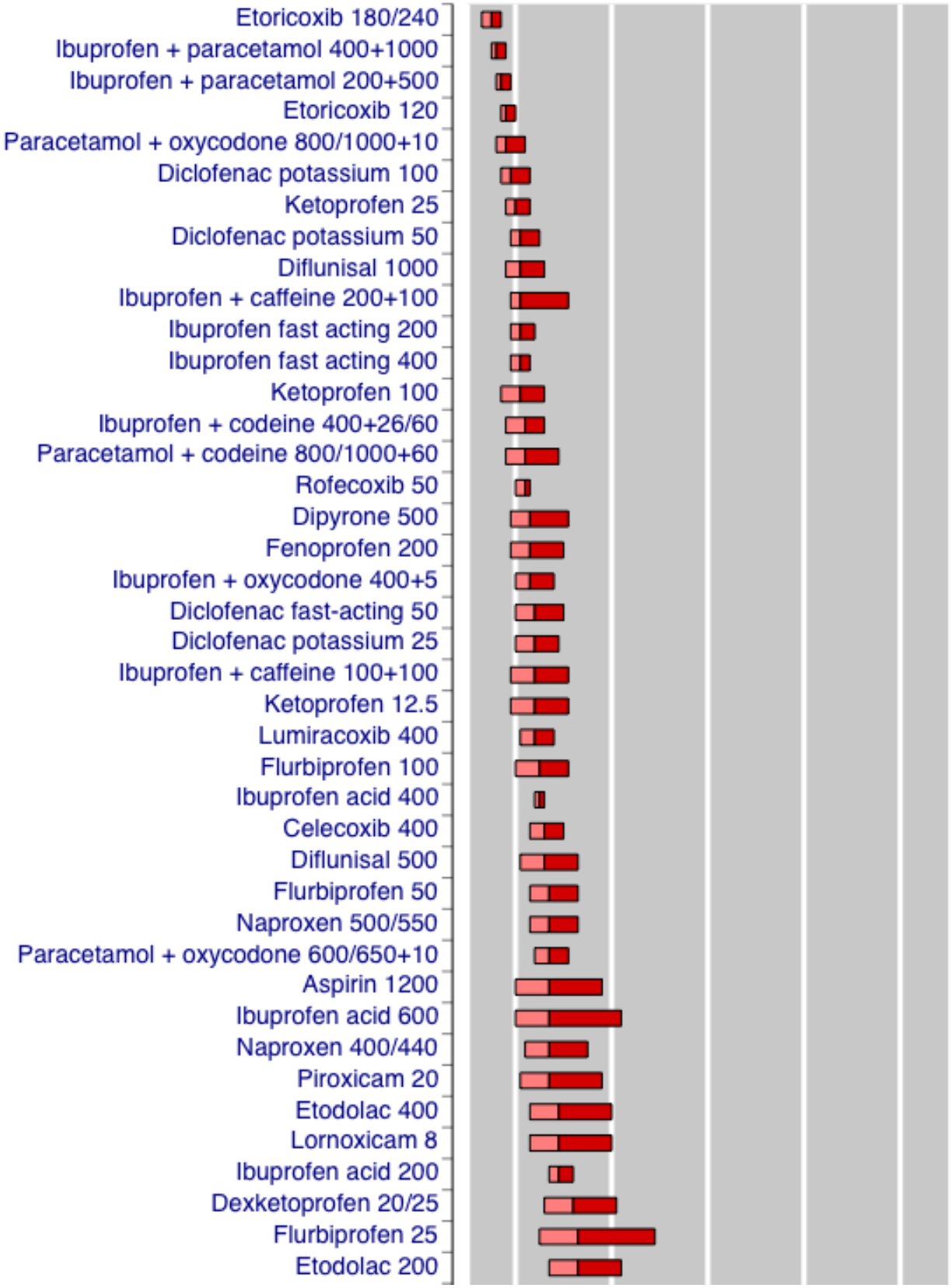
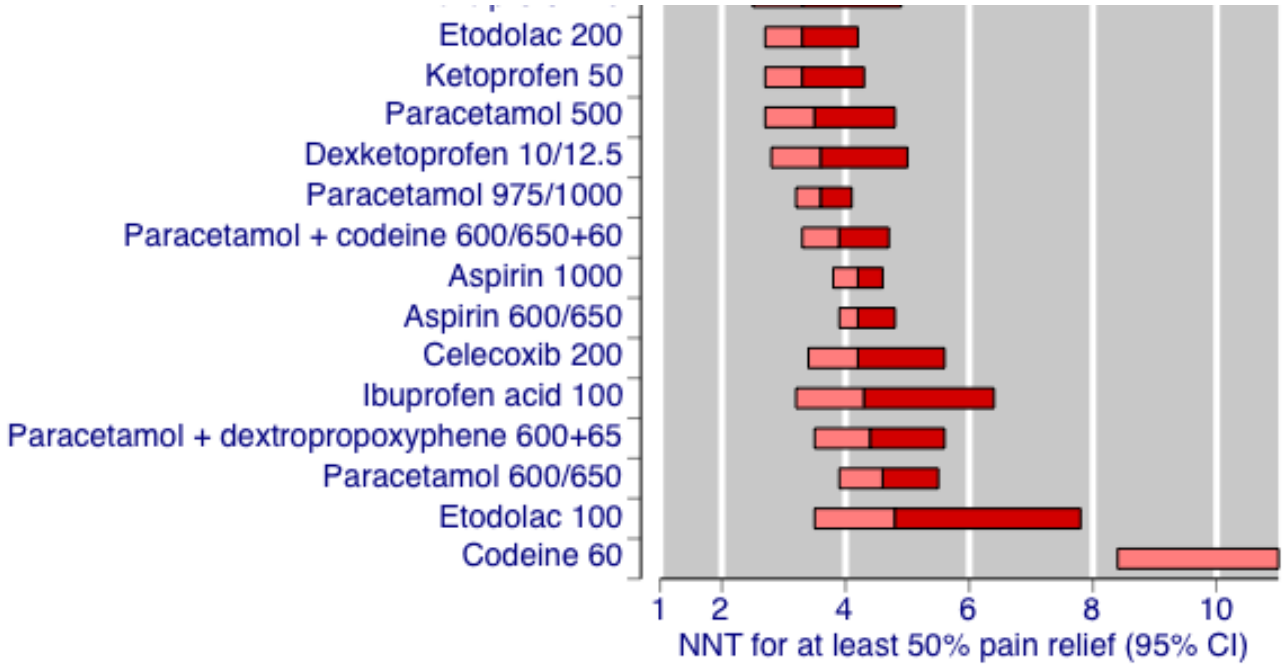


Figure 1. (Continued)



The number of participants was high (above 2000) with ibuprofen acid 400 mg and 200 mg, aspirin 600/650 mg, paracetamol 975/1000 mg, and rofecoxib 50 mg. Results involving high numbers of participants and low (good) NNTs were particularly robust, with almost 20,000 participants needed in zero effect studies to overturn the result for ibuprofen 400 mg and over 13,000 to overturn that for rofecoxib 50 mg.

NNTs varied from as low as 1.5 for the combination of ibuprofen 400 mg plus paracetamol 1000 mg to as high as 12 for codeine 60 mg. The majority of pairs of drug and dose had NNTs below 3. Higher doses of the same drug tended to have lower (better) NNTs, although this was not particularly evident with paracetamol.

Summary table B: Results judged to be reliable

Drug	Dose (mg)	Number of		At least 50% maximum pain relief over 4 - 6 hours						Susceptibility to publication bias
				Number with outcome/total		Percent with outcome		Risk ratio (95% CI)	NNT (95% CI)	
		Studies	Participants	Active	Placebo	Active	Placebo			
Aspirin	600/650	65	4965	983/2496	379/2469	39	15	2.5 (2.3 to 2.8)	4.2 (3.8 to 4.6)	6856
Aspirin	1000	6	618	138/340	40/278	41	14	2.7 (2.0 to 3.7)	4.2 (3.8 to 4.6)	853
Aspirin	1200	3	249	85/140	25/109	62	19	3.3 (1.8 to 6.3)	2.4 (1.9 to 3.2)	789
Celecoxib	200	4	705	149/423	32/282	35	11	3.5 (2.4 to 5.1)	4.2 (3.4 to 5.6)	974
Celecoxib	400	5	722	202/466	12/256	43	5	10 (5.7 to 18)	2.6 (2.3 to 3.0)	2055
Codeine	60	33	2411	311/1199	209/1212	26	17	1.5 (1.3 to 1.7)	12 (8.4 to 18)	NNT above 10
Dexketoprofen	10/12.5	5	452	104/230	38/222	45	17	2.7 (2.0 to 3.7)	3.6 (2.8 to 5.0)	804
Dexketoprofen	20/25	6	523	129/225	38/248	47	15	3.3 (2.4 to 4.5)	3.2 (2.6 to 4.1)	1111
Diclofenac fast acting	50	4	486	156/214	46/232	61	20	2.9 (3.2 to 3.8)	2.4 (2.0 to 3.0)	1539
Diclofenac potassium	25	4	502	140/248	37/274	56	15	3.9 (2.8 to 5.3)	2.4 (2.0 to 2.9)	1590
Diclofenac potassium	50	7	757	253/398	60/359	64	17	3.7 (2.9 to 4.7)	2.1 (1.9 to 2.5)	2848
Diclofenac potassium	100	6	589	196/300	39/289	65	13	4.8 (3.6 to 6.5)	1.9 (1.7 to 2.3)	2511
Diflunisal	500	6	391	104/198	27/193	53	14	3.8 (2.6 to 5.4)	2.6 (2.1 to 3.3)	1113
Diflunisal	1000	5	357	112/182	26/175	62	15	4.1 (2.9 to 6.0)	2.1 (1.8 to 2.6)	1343

Dipyrone	500	5	288	106/143	45/145	74	31	2.4 (1.8 to 3.1)	2.3 (1.9 to 3.1)	964
Etodolac	100	5	498	103/251	50/247	41	20	2.0 (1.5 to 2.7)	4.8 (3.5 to 7.8)	540
Etodolac	200	7	670	145/333	44/337	44	13	3.3 (2.5 to 4.5)	3.3 (2.7 to 4.2)	1360
Etodolac	400	3	222	52/134	4/88	39	5	9.0 (3.4 to 24)	2.9 (2.3 to 4.0)	544
Etoricoxib	120	6	798	332/503	34/295	66	12	5.6 (4.0 to 7.8)	1.8 (1.7 to 2.0)	3635
Etoricoxib	180/240	2	199	129/150	6/49	79	12	6.4 (3.1 to 14)	1.5 (1.3 to 1.7)	1128
Fenoprofen	200	4	287	83/146	19/141	57	13	4.2 (2.7 to 6.4)	2.3 (1.9 to 3.0)	961
Flurbiprofen	25	3	208	36/102	5/106	35	5	7.0 (2.9 to 16)	3.3 (2.5 to 4.9)	422
Flurbiprofen	50	10	692	245/353	108/339	69	32	2.2 (1.9 to 2.6)	2.7 (2.3 to 3.3)	1871
Flurbiprofen	100	7	416	139/215	48/201	65	24	2.8 (2.2 to 3.6)	2.5 (2.0 to 3.1)	1248
Ibuprofen acid	100	4	396	60/192	16/204	31	8	3.7 (2.3 to 5.9)	4.3 (3.2 to 6.4)	525
Ibuprofen acid	200	18	2103	448/1094	67/1009	41	7	6.5 (5.1 to 8.2)	2.9 (2.7 to 3.2)	5149
Ibuprofen acid	400	51	5604	1596/3070	289/2543	52	12	4.6 (4.0 to 5.1)	2.5 (2.4 to 2.6)	16,812
Ibuprofen acid	600	3	203	88/114	36/89	77	40	2.0 (1.5 to 2.6)	2.7 (2.0 to 4.2)	549
Ibuprofen fast acting	200	7	828	270/478	34/350	57	10	5.7 (4.2 to 7.9)	2.1 (1.9 to 2.4)	3115
Ibuprofen fast acting	400	13	1364	427/658	85/466	65	18	3.9 (3.2 to 4.7)	2.1 (1.9 to 2.3)	5131
Ibuprofen + caffeine	100+100	2	200	43/99	0/101	43	0	45 (36.3 to 320)	2.4 (1.9 to 3.1)	633
Ibuprofen + caffeine	200+100	4	334	103/174	16/160	59	10	5.5 (3.5 to 8.7)	2.1 (1.9 to 3.1)	1256
Ibuprofen + codeine	400+26-60	4	443	178/276	30/167	64	18	4.1 (2.8 to 5.9)	2.2 (1.8 to 2.6)	1571
Ibuprofen + paracetamol	200+500	3	508	240/349	10/159	69	6	10 (5.7 to 19)	1.6 (1.5 to 1.8)	2667
Ibuprofen + paracetamol	400+1000	3	543	278/384	10/159	72	6	11 (6.2 to 20)	1.5 (1.4 to 1.7)	3077
Ibuprofen + oxycodone	400+5	3	603	250/418	31/185	60	17	3.6 (2.6 to 5.1)	2.3 (2.0 to 2.8)	2019

Ketoprofen	12.5	3	274	77/138	18/136	56	13	4.2 (2.7 to 6.6)	2.4 (1.9 to 3.1)	868
Ketoprofen	25	8	535	175/281	31/254	62	12	4.9 (3.5 to 6.9)	2.0 (1.8 to 2.3)	2140
Ketoprofen	50	8	624	151/314	56/310	48	18	2.7 (2.0 to 3.5)	3.3 (2.7 to 4.3)	1267
Ketoprofen	100	5	321	106/161	28/160	66	18	3.6 (2.5 to 5.1)	2.1 (1.7 to 2.6)	1208
Lornoxicam	8	3	273	71/155	13/118	46	11	4.7 (2.7 to 8.1)	2.9 (2.3 to 4.0)	668
Lumiracoxib	400	4	578	183/366	17/212	50	8	6.9 (4.1 to 11)	2.4 (2.1 to 2.8)	1830
Naproxen	400/440	3	334	103/210	14/124	49	11	4.8 (2.8 to 8.4)	2.7 (2.2 to 3.5)	903
Naproxen	500/550	9	784	200/394	59/390	52	15	3.4 (2.6 to 4.4)	2.7 (2.3 to 3.3)	2120
Paracetamol	500	6	561	176/290	86/271	61	32	1.9 (1.6 to 2.3)	3.5 (2.7 to 4.8)	1042
Paracetamol	600/650	19	1886	358/954	145/932	38	16	2.4 (2.0 to 2.8)	4.6 (3.9 to 5.5)	2214
Paracetamol	975/1000	28	3232	876/1906	241/1329	46	18	2.7 (2.4 to 3.0)	3.6 (3.2 to 4.1)	5746
Paracetamol + codeine	600/650+60	17	1413	370/857	96/556	43	17	2.6 (2.2 to 3.2)	3.9 (3.3 to 4.7)	2210
Paracetamol + codeine	800/1000+80	3	192	64/121	5/71	53	7	6.3 (2.9 to 14)	2.2 (1.8 to 2.9)	681
Paracetamol + dextro-propoxyphene	65+650	6	963	184/478	74/485	38	15	2.5 (2.0 to 3.2)	4.4 (3.5 to 5.6)	1226
Paracetamol + oxycodone	650+10	10	1043	346/680	49/363	51	14	3.9 (2.9 to 5.2)	2.7 (2.4 to 3.1)	2820
Paracetamol + oxycodone	1000+10	2	289	100/147	19/142	68	13	4.9 (3.2 to 7.6)	1.8 (1.6 to 2.2)	1317
Piroxicam	20	3	280	89/141	36/139	63	26	2.5 (1.8 to 3.3)	2.7 (2.1 to 3.8)	757
Rofecoxib	50	25	3688	1458/2519	134/1169	58	11	5.1 (4.3 to 6.1)	2.2 (2.0 to 2.3)	13,076

6. Percentage of participants achieving target of at least 50% maximum pain relief

Summary table B provides information on the percentage of participants achieving the outcome of at least 50% of maximum pain relief with analgesic and placebo. There was very wide variation between drugs, and some variation in responses with placebo, though most fell between 5% and 15%.

7. Time to remedication

A number of reviews reported the mean of the mean or median time to remedication, a useful secondary outcome indicating the duration of effective analgesia before the pain intensifies to the point where additional analgesia is required. For placebo, averaging over all reviews, the mean time to remedication was two hours; trials typically have a one- to two-hour period before which additional analgesia is not allowed, to allow time for any analgesic to work. For analgesics the mean duration varied between below two to three hours for gabapentin 250 mg and codeine 60 mg, and up to 20 hours for etoricoxib 120 mg (Figure 2). Analgesics with a low NNT tended to have a longer duration of action (Figure 3).

Figure 2. Mean or median time to remedication.

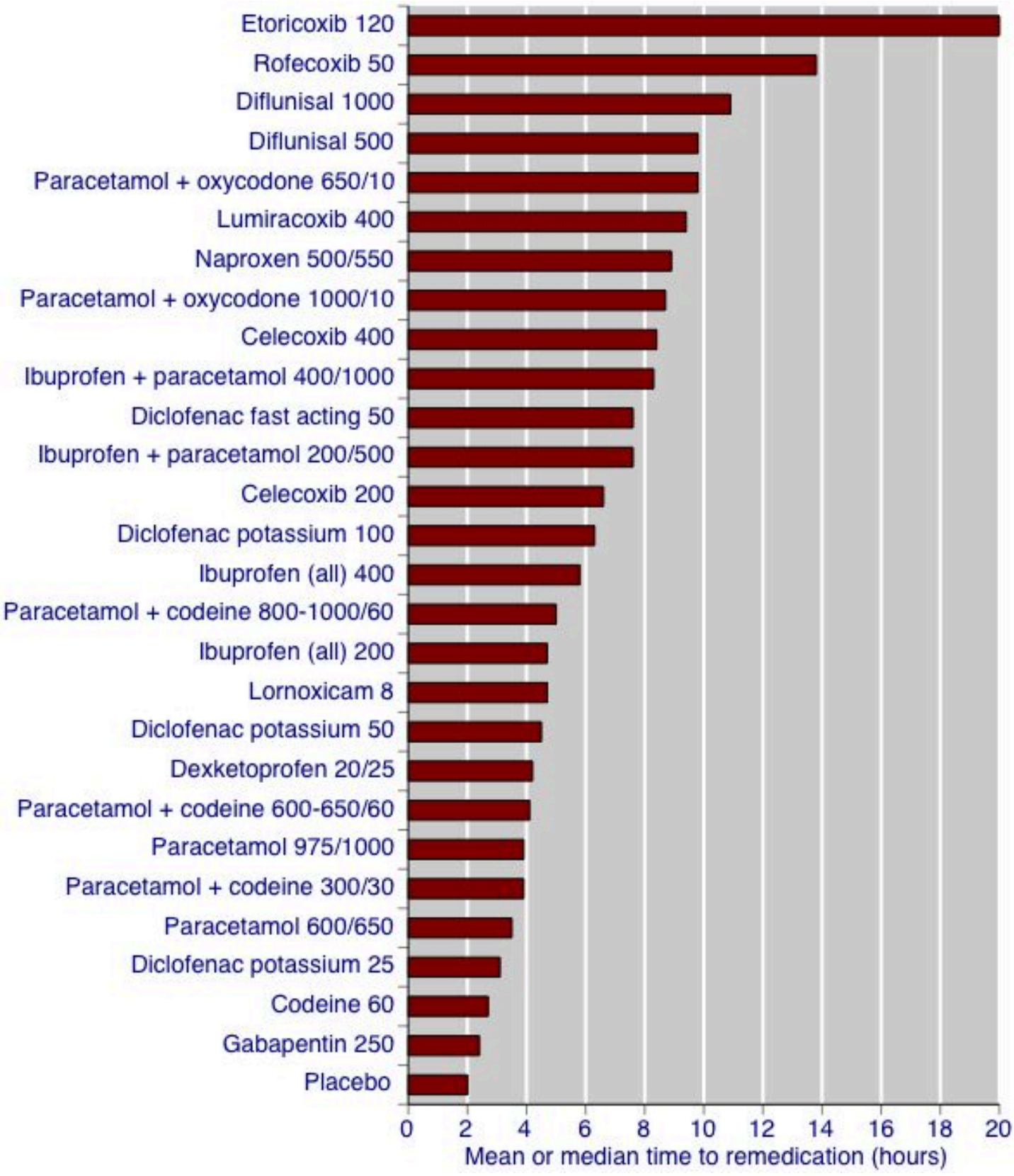
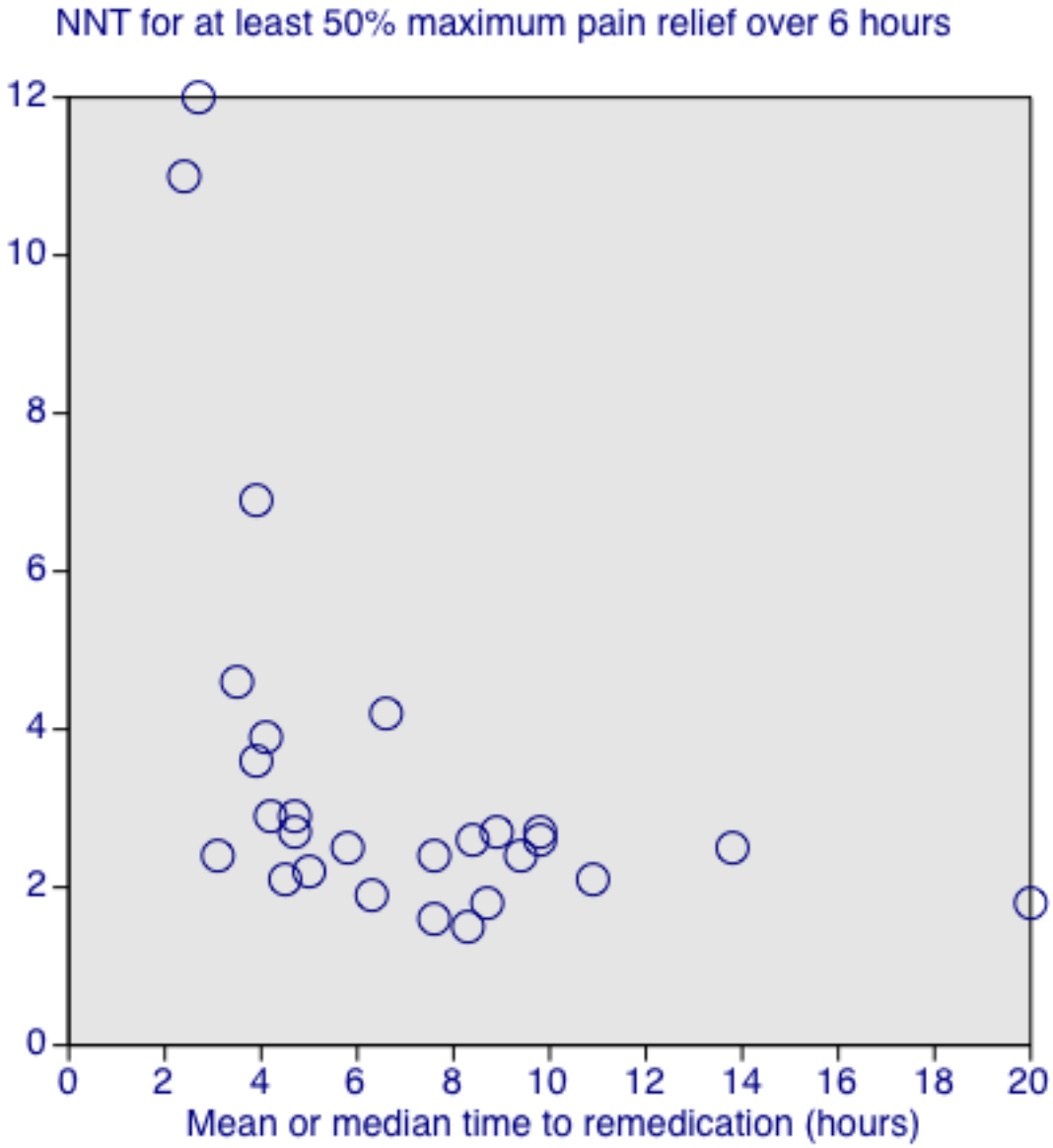


Figure 3. Relationship between NNT over four to six hours and time to remedication in individual drugs.



8. Percentage remedicating

We also collected information on the percentage of participants receiving active treatment and placebo who had remedicated at various times after the start of therapy. This was sparsely reported in a small subsection of studies. The percentage of participants remedicating with active drug was usually much lower than the percentage remedicating with placebo, both in studies lasting eight hours (Figure 4) and six hours (Figure 5).

Figure 4. Percentage remedicating within eight hours with active and placebo. Lines connect review results for active drugs and placebo.

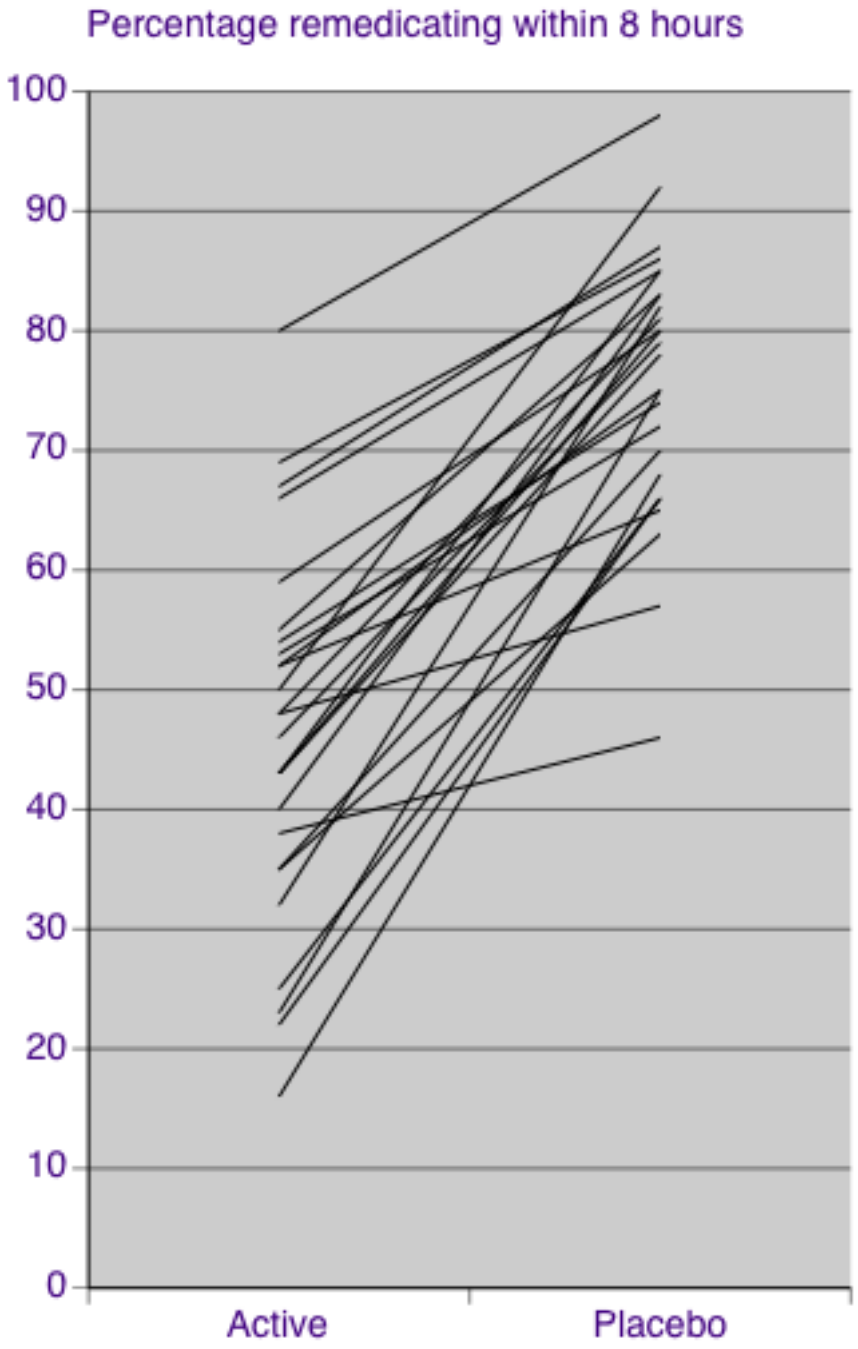
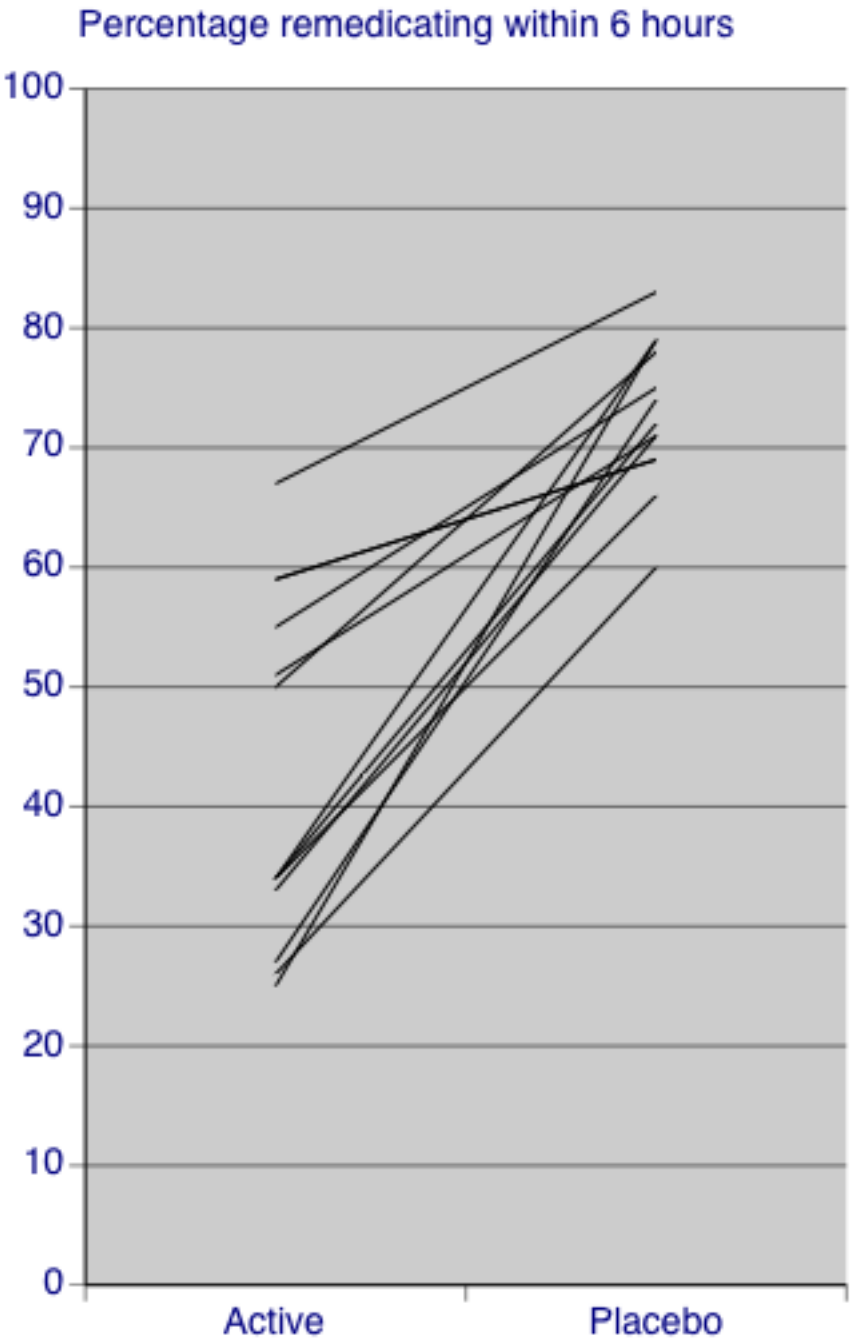


Figure 5. Percentage remedicating within six hours with active and placebo. Lines connect review results for active drugs and placebo.



DISCUSSION

Summary of main results

We have reliable efficacy estimates for 53 pairs of drug and dose in all types of surgery: this is 10 more than in the previous version of this overview review, due to the inclusion of more fixed dose combination analgesics, and a recognition that different formulations of the same drug can produce markedly different analgesic efficacy in acute pain. The estimates of efficacy have all been obtained using essentially the same clinical trial methods since they were first set out (Beecher 1957), and both trial and review methods have been standardised based on good evidence. The original philosophy concerning acute pain trials has been tested subsequently in a number of analyses using individual participant data (McQuay 2012; Moore 1997c; Moore 2005; Moore 2011b), and those and other analyses also underpin the trials and reviews. This makes the results of studies comparable, and that has previously included finding no significant difference between different pain models (Barden 2004), and no noticeable effect of study sponsorship (Barden 2006).

The most striking difference between this overview and the previous version resulted from increased information about fixed dose combination analgesics, and about different formulations, particularly fast acting formulations. Both provided some of the more effective analgesics. For example, ibuprofen 200 mg plus paracetamol 500 mg had an NNT of 1.5, ibuprofen 200 mg plus caffeine 100 mg had an NNT of 2.1, as did ibuprofen 200 mg in a fast acting formulation or diclofenac potassium 50 mg, another fast acting formulation. This demonstrates that factors beyond drug and dose play major parts in producing good analgesia, and that good analgesia can be generated by lower doses of drugs used hitherto; this has an important potential safety implication, particularly at the population level.

We also know that there are a number of drugs for which there are no available trial data on their effectiveness in acute pain (Acemetacin 2009; Meloxicam 2009; Nabumetone 2009; Nefopam 2009; Sulindac 2009; Tenoxicam 2009; Tiaprofenic acid 2009), as well as pairs of drug and dose with definite evidence of no benefit, inadequate evidence of benefit, or evidence of benefit that is unreliable.

Placebo responses in the different meta-analyses - the percentage of people achieving at least 50% maximum pain relief with placebo over four to six hours - were reasonably consistent, with most falling between 5% and 20%. The degree of variability is what is expected by the random play of chance when numbers of participants is small (Moore 1998).

The results show clearly that even the most effective drugs fail to deliver good analgesia to a proportion of people, meaning that a degree of analgesic failure is to be expected. Figure 2 shows that with many interventions, it is to be expected in more than half of people treated.

There was also an interesting relationship between efficacy over four to six hours and duration of analgesia measured by mean time to remedication (Figure 3). Drugs with short duration of action tended to have higher (worse) NNTs, while drugs with longer duration of action had universally lower (better) NNTs, typically of two or below in those where mean remedication time was eight hours or longer. While not unexpected, this relationship implies that drugs with longer effects are likely to be more useful and effective in clinical practice.

Overall completeness and applicability of evidence

The 39 Cochrane reviews cover almost all oral analgesics, although throughout the world many different combination analgesics can be found, typically without any published clinical trials. The review found that for seven drugs there were no clinical trial data and for a further 10 drugs there was inadequate information for any reliable basis of efficacy. In both these cases there are probably unpublished clinical trials. The authors' (unpublished) experience is that obtaining clinical trial data for older drugs is difficult and often impossible - although not always, as demonstrated by the eventual publication of 14 unpublished clinical trials of tramadol in a meta-analysis (Moore 1997c). None of the drugs or doses for which this was a concern are used commonly in treating acute pain.

Some reviews appear not to be recent; all had been updated since 2008, but without finding any new studies and so they have kept their original citation dates (Dihydrocodeine 2000; Paracetamol ± dextropropoxyphene 1999; Piroxicam 2000). The review on ibuprofen requires an urgent update because it only partially reflects the change in emphasis on fast acting formulations, and because more information on fast acting formulations continues to be published. Indeed, there are arguments for splitting some reviews by formulation.

There are no Cochrane reviews for some commonly used drugs. These include tramadol, though non-Cochrane reviews are available for these (Edwards 2002; Moore 1997c), which used the same methods and standards as the Cochrane reviews, but results of these have not been included in the comparative figures. For completeness, results for these non-Cochrane reviews are shown in Summary table C.

The results for tramadol 50 mg in dental pain and for tramadol 100 mg in other painful conditions are clearly not reliable, as they are subject to potential publication bias. Results for higher doses of tramadol and tramadol plus paracetamol are reliable. It is worth noting that reviews of tramadol indicated high rates of adverse events, though they were not reported in ways comparable to Cochrane reviews (Edwards 2002; Moore 1997c).

While much of the information in the overview derives from the third molar extraction model, previous analyses have shown no difference between efficacy in that pain model in typically younger participants, and other postsurgical models where the participants are often older, and probably less healthy. Relative efficacy from acute pain is typically maintained in acute and chronic pain conditions, as with ibuprofen and paracetamol (Moore 2015c).

Summary table C: Data from non-Cochrane reviews

Drug	Dose (mg)	Pain condition	Number of		At least 50% maximum pain relief over 4-6 hours						Susceptibility to publication bias
					Number on		Percent with outcome		Risk ratio (95% CI)	NNT (95% CI)	
			Studies	Participants	Active	Placebo	Active	Placebo			
Tramadol	50	Dental	6	471	41/246	13/225	17	6	2.9 (1.6 to 5.2)	9.1 (6.1 to 19)	47
Tramadol	100	Dental	7	578	89/300	22/278	30	8	3.8 (2.4 to 5.8)	4.6 (3.6 to 6.4)	679
Tramadol	100	Other surgery	4	304	51/168	13/136	30	10	3.2 (1.8 to 5.6)	4.8 (3.4 to 8.2)	329
Tramadol	150	Other surgery	5	371	106/184	31/187	60	17	3.5 (2.4 to 4.9)	2.4 (2.0 to 3.1)	1175
Tramadol + paracetamol	75/650	Dental	5	659	128/340	11/339	40	3	12 (6.4 to 21)	2.9 (2.5 to 3.5)	1613

Quality of the evidence

The quality of the evidence was good, using standard reviews examining standard clinical trials designed to measure the analgesic efficacy of drugs in sensitive assays in acute painful conditions (McQuay 2012). The overview process further removed any results likely to be the object of potential publication bias, so that only reliable results remained. This leaves a very large body of efficacy results presented by dose and formulation.

These results report a clinically useful level of pain relief over a sensible period, and with the common comparator of placebo. Although indirect comparisons are often criticised, this is one circumstance where indirect comparison can be justified because of the clinical homogeneity of trials and outcomes, and because data like these have been tested and indirect comparison found to be a reasonable approach (Song 2003).

Potential biases in the overview process

No obvious biases in the overview process exist, for the reasons given above.

Small data sets are clearly more variable than larger data sets, as would be expected (Moore 1998). However, with few exceptions, placebo response rates were within limited ranges, typically between 5% and 20%.

Most studies in the individual reviews will have been sponsored or conducted by manufacturers. This is not likely to be a source of any bias, since specific analyses have been conducted on some of the larger data sets to demonstrate that no industry bias exists in like-for-like comparisons (Barden 2006).

Agreements and disagreements with other studies or reviews

The only other overview of this type known to exist for acute pain studies is a non-Cochrane overview in dental pain (Barden 2004). The general methods used were similar and there were no major differences.

Other important issues

This overview has brought together information on a very large number of participants and studies that have had one aim, namely to test whether a particular drug at a particular dose had analgesic properties. The basic design of the individual studies was developed in the 1950s and 1960s, and rigorously tested at the time when randomised and double-blind studies were needed for objective assessment of analgesic efficacy (Houde 1960). Even the earliest studies emphasised large individual variability, and the variability in treatment groups of small size (Keats 1950).

These methods of analgesic testing have, with little change, become the standard way of demonstrating that a drug is an analgesic, and are typically performed early in the development of any new pain-relieving drug. A number of individual participant analyses have examined various aspects of their design, conduct, and reporting (Barden 2004; Barden 2006; Moore 1997c; Moore 2005; Moore 2011b; Moore 2014; Moore 2015a). All of these investigations confirmed the success of the model, though adverse event reporting was inadequate (Edwards 1999). Other individual participant analyses of the postoperative period have demonstrated that participant satisfaction is highly correlated with good pain relief, showing the value of the outcome of at least 50% maximum pain relief (Mhuircheartaigh 2009). An important factor is that these studies, as best can be judged, were conducted in participants who were fasting; taking analgesics with food can have a major impact on the speed of absorption, and probably effect (Moore 2015b).

While the reviews in this overview provide an excellent assessment of analgesic efficacy, both in the fact of the effects and often in its magnitude, there remains a distinction between measurement in trials and effectiveness in the clinic, and for different types of acute pain. Relative efficacy is, however, maintained between different painful conditions. For example, in dental pain ibuprofen 400 mg (NNT 2.3) is better than paracetamol 1000 mg (3.2) and aspirin 1000 mg (4.2), and this is maintained in other painful conditions (Moore 2015c). Information about analgesic efficacy from individual systematic reviews and overviews can be incorporated into schema for effective management of acute pain (Frampton 2009), or applied to other acute painful conditions.

It is the case that many of the individual studies used both a placebo and an active comparator. However, the actual drug and dose of active comparator varied so widely that useful direct comparisons between any two drugs was not available. Despite the fact that indirect comparisons have been shown to be reliable where sufficient high-quality data existed (Song 2003), one further step might be taken. That step would involve the use of network meta-analysis to confirm the assessment of relative efficacy in the overview, and to explore further methodological issues in this highly standardised and homogeneous data set (Caldwell 2005; Salanti 2008).

One further point is that of dose-response. In these studies there may be examples where higher doses do not show greater effect. For example, ibuprofen acid 600 mg had a point estimate NNT of 2.7, while for 400 mg it was 2.5. The reason may be in case mix, with a very large amount of trial data for the 400 mg dose and a relatively modest amount for 600 mg, often from different studies. Dose response has been shown in more detailed direct comparison of doses across a range of analgesics in acute postoperative pain (McQuay 2007).

AUTHORS' CONCLUSIONS

Implications for practice

For people with acute pain

The major implication for people with acute pain is the knowledge that there is a body of reliable evidence about the efficacy of 53 pairs of drug and dose in acute pain. Not every person will achieve good pain relief even with the most effective drugs, and analgesic failure is to be expected with a single dose, or perhaps with particular drugs in particular people. Failure to achieve good pain relief should not be acceptable because it is likely that failure with any one drug could be reversed with another.

For clinicians

The major implication for clinicians is the knowledge that there is a body of reliable evidence about the efficacy of 53 pairs of drug and dose in acute pain. These results include information of immediate practical relevance including the percentage of people likely to benefit in the short term, and comparative information about

the likely duration of effect - a matter of pragmatic importance. However, not every person will achieve good pain relief even with the most effective drugs, and analgesic failure is to be expected with a single dose, or perhaps with particular drugs in particular people. Failure to achieve good pain relief should be actively and regularly sought and rectified.

There is also a clear message that simple drug combinations and fast acting formulations can deliver good analgesia in many people with acute pain at relatively low doses.

While much of the information in the overview derives from the third molar extraction model, previous analyses have shown no difference between efficacy in that pain model in typically younger participants, and other postsurgical models where the participants are older, and probably less healthy.

For policy makers

The issue is not which drug, but achieving success - good pain relief is the goal of treatment. Surveys over a long period have shown that acute pain generally, and particularly in hospital, is poorly treated, and that many people experience moderate or severe pain.

Simple drug combinations and fast acting formulations can deliver good analgesia at relatively low doses in many people with acute pain. Acute pain treatment is often part of a complex of interactions between the person, condition, and desired outcome; the overview helps by presenting evidence from which rational choices and decisions can be made. The evidence linking short term benefit with longer duration of action is particularly important in this regard.

For funders

Very high levels of efficacy are available from a number of drugs and formulations, at relatively low doses, that are relatively inexpensive. This contrasts with anecdotal evidence that less effective drugs and formulations are frequently used because they are considered less expensive. It is not clear that this is sensible.

Implications for research

General

The studies in this overview have been single dose studies designed to demonstrate that analgesic drugs work in reducing pain. These trials were principally performed for regulatory purposes. An arguably more appropriate approach is to have studies examining treatment of acute pain over days rather than hours. Studies of that type are rare. Average pain, as reported in most individual studies, is unhelpful.

Design

There are no main issues over the design of single dose studies, but considerable issues over reporting and outcomes. Despite calls over at least a decade to use participant-centred outcomes such as number of participants with no worse than mild pain, the principal outcomes reported are still statistical.

Measurement (end points)

Pain measurement is not an issue.

Other

Many of the improvements in understanding acute pain have been derived from individual participant level analyses. These can only come from close cooperation with the pharmaceutical industry, which overwhelmingly funds the studies and 'owns' the data. Industry has a responsibility to perform more useful analyses than just those required for regulatory purposes.

Possibly the main implication for research is methodological. There will be few circumstances where such a body of information exists in such a clinically homogeneous data set and it might appear to be an ideal opportunity to test new methods in meta-analyses, such as network meta-analyses.

A C K N O W L E D G E M E N T S

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REFERENCES

References to included reviews

Aceclofenac 2009

Moore RA, Derry S, McQuay HJ. Single dose oral aceclofenac for postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD007588.pub2]

Acemetacin 2009

Moore RA, Derry S, McQuay HJ. Single dose oral acemetacin for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD007589.pub2]

Aspirin 2012

Derry S, Moore RA. Single dose oral aspirin for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 4. [DOI: 10.1002/14651858.CD002067.pub2]

Celecoxib 2013

Derry S, Moore RA. Single dose oral celecoxib for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2013, Issue 10. [DOI: 10.1002/14651858.CD004233.pub4]

Codeine 2010

Derry S, Moore RA, McQuay HJ. Single dose oral codeine, as a single agent, for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 4. [DOI: 10.1002/14651858.CD008099.pub2]

Dexibuprofen 2009

Moore RA, Derry S, McQuay HJ. Single dose oral dexibuprofen [S(+)-ibuprofen] for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD007550.pub2]

Diclofenac 2015

Moore RA, Derry S, Wiffen PJ. Single dose oral diclofenac for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2015, Issue 7. [DOI: 10.1002/14651858.CD004768.pub3]

Diflunisal 2010

Wasey JO, Derry S, Moore RA, McQuay HJ. Single dose oral diflunisal for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 4. [DOI: 10.1002/14651858.CD007440.pub2]

Dihydrocodeine 2000

Moore RA, Rees J, Derry S, McQuay HJ. Single dose oral dihydrocodeine for acute postoperative pain. *Cochrane Database of Systematic Reviews* 2000, Issue 2. [DOI: 10.1002/14651858.CD002760]

Dipyrone 2010

Edwards J, Meseguer F, Faura C, Moore RA, McQuay HJ, Derry S. Single dose dipyrone for acute postoperative pain. *Cochrane Database of Systematic Reviews* 2010, Issue 9. [DOI: 10.1002/14651858.CD003227.pub2]

Etodolac 2009

Tirunagari SK, Derry S, Moore RA, McQuay HJ. Single dose oral etodolac for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD007357.pub2]

Etoricoxib 2014

Clarke R, Derry S, Moore RA. Single dose oral etoricoxib for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2014, Issue 5. [DOI: 10.1002/14651858.CD004309.pub4]

Fenbufen 2009

Moore RA, Derry S, McQuay HJ. Single dose oral fenbufen for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD007547.pub2]

Fenoprofen 2011

Traa MX, Derry S, Moore RA. Single dose oral fenoprofen for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2011, Issue 2. [DOI: 10.1002/14651858.CD007556.pub2]

Flurbiprofen 2009

Sultan A, McQuay HJ, Moore RA, Derry S. Single dose oral flurbiprofen for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD007358.pub2]

Gabapentin 2010

Straube S, Derry S, Moore RA, Wiffen PJ, McQuay HJ. Single dose oral gabapentin for established acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 5. [DOI: 10.1002/14651858.CD008183.pub2]

Ibuprofen + caffeine 2015

Derry S, Wiffen PJ, Moore RA. Single dose oral ibuprofen plus caffeine for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2015, Issue 7. [DOI: 10.1002/14651858.CD011509.pub2]

Ibuprofen + codeine 2015

Derry S, Karlin S, Moore RA. Single dose oral ibuprofen plus codeine for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2015, Issue 2. [DOI: 10.1002/14651858.CD010107.pub3]

Ibuprofen + oxycodone 2013

Derry S, Derry CJ, Moore RA. Single dose oral ibuprofen plus oxycodone for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2013, Issue 6. [DOI: 10.1002/14651858.CD010289.pub2]

Ibuprofen + paracetamol 2013

Derry CJ, Derry S, Moore RA. Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain. *Cochrane Database of Systematic Reviews* 2013, Issue 6. [DOI: 10.1002/14651858.CD010210.pub2]

Ibuprofen 2009

Derry C, Derry S, Moore RA, McQuay HJ. Single dose oral ibuprofen for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD001548.pub2]

Indometacin 2004

Moore RA, Derry S, Mason L, McQuay HJ, Rees J. Single dose oral indometacin for the treatment of acute postoperative pain. *Cochrane Database of Systematic Reviews* 2004, Issue 4. [DOI: 10.1002/14651858.CD004308.pub2]

Ketoprofen and dexketoprofen 2009

Barden J, Derry S, McQuay HJ, Moore RA. Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD007355.pub2]

Lornoxicam 2009

Hall PE, Derry S, Moore RA, McQuay HJ. Single dose oral lornoxicam for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD007441.pub2]

Lumiracoxib 2010

Roy YM, Derry S, Moore RA. Single dose oral lumiracoxib for postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 7. [DOI: 10.1002/14651858.CD006865.pub2]

Mefenamic acid 2011

Moll R, Derry S, Moore RA, McQuay HJ. Single dose oral mefenamic acid for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2011, Issue 3. [DOI: 10.1002/14651858.CD007553.pub2]

Meloxicam 2009

Moore RA, Derry S, McQuay HJ. Single dose oral meloxicam for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD007552.pub2]

Nabumetone 2009

Moore RA, Derry S, Moore M, McQuay HJ. Single dose oral nabumetone for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD007548.pub2]

Naproxen 2009

Derry C, Derry S, Moore RA, McQuay HJ. Single dose oral naproxen and naproxen sodium for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: 10.1002/14651858.CD004234.pub3]

Nefopam 2009

Kakkar M, Derry S, Moore RA, McQuay HJ. Single dose oral nefopam for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD007442.pub2]

Paracetamol + codeine 2009

Toms L, Derry S, Moore RA, McQuay HJ. Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: 10.1002/14651858.CD001547.pub2]

Paracetamol 2008

Toms L, McQuay HJ, Derry S, Moore RA. Single dose oral paracetamol (acetaminophen) for postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD004602.pub2]

Paracetamol ± dextropropoxyphene 1999

Moore RA, Collins S, Rees J, Derry S, McQuay HJ. Single dose oral dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain. *Cochrane Database of Systematic Reviews* 1999, Issue 1. [DOI: 10.1002/14651858.CD001440]

Paracetamol ± oxycodone 2009

Gaskell H, Derry S, Moore RA, McQuay HJ. Single dose oral oxycodone and oxycodone plus paracetamol (acetaminophen) for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD002763.pub2]

Piroxicam 2000

Moore RA, Rees J, Loke Y, Derry S, McQuay HJ. Single dose oral piroxicam for acute postoperative pain. *Cochrane Database of Systematic Reviews* 2000, Issue 2. [DOI: 10.1002/14651858.CD002762]

Rofecoxib 2009

Bulley S, Derry S, Moore RA, McQuay HJ. Single dose oral rofecoxib for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD004604.pub3]

Sulindac 2009

Moore RA, Derry S, McQuay HJ. Single dose oral sulindac for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD007540.pub2]

Tenoxicam 2009

Moore OA, McIntyre M, Moore RA, Derry S, McQuay HJ. Single dose oral tenoxicam for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD007591.pub2]

Tiaprofenic acid 2009

Moore RA, Derry S, Moore M, McQuay HJ. Single dose oral tiaprofenic acid for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD007542.pub2]

Additional references

Barden 2004

Barden J, Edwards JE, McQuay HJ, Moore RA. Pain and analgesic response after third molar extraction and other postsurgical pain. *Pain* 2004;**107**(1-2):86-90. [DOI: 10.1016/j.pain.2003.09.021]

Barden 2006

Barden J, Derry S, McQuay HJ, Moore RA. Bias from industry trial funding? A framework, a suggested approach, and a negative result. *Pain* 2006;**121**(3):207-18. [DOI: doi:10.1016/j.pain.2005.12.011]

Beecher 1957

Beecher HK. The measurement of pain; prototype for the quantitative study of subjective responses. *Pharmacology Reviews* 1957;**9**:59-209.

Botting 2000

Botting RM. Mechanism of action of acetaminophen: is there a cyclooxygenase 3?. *Clinical Infectious Diseases* 2000;**31**(5):S203-10. [DOI: 10.1086/317520]

Caldwell 2005

Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 2005;**331**:897-900. [DOI: 10.1136/bmj.331.7521.897]

Chandrasekharan 2002

Chandrasekharan NV. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure and expression. *Proceedings of the National Academy of Sciences of the United States of America* 2002;**99**:13926-31. [DOI: 10.1073/pnas.162468699]

Collins 1997

Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimetres?. *Pain* 1997;**72**:95-7. [DOI: 10.1016/S0304-3959(97)00005-5]

Edwards 1999

Edwards JE, McQuay HJ, Moore RA, Collins SL. Reporting of adverse effects in clinical trials should be improved: lessons from acute postoperative pain. *Journal of Pain and Symptom Management* 1999;**18**(6):427-37. [DOI: 10.1093/bja/aep300]

Edwards 2002

Edwards JE, McQuay HJ, Moore RA. Combination analgesic efficacy: individual patient data meta-analysis of single-dose oral tramadol plus acetaminophen in acute postoperative pain. *Journal of Pain Symptom Management* 2002;**23**:121-30. [DOI: 10.1002/14651858.CD002067]

FitzGerald 2001

FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *New England Journal of Medicine* 2001;**345**(6):433-42. [DOI: 10.1056/NEJM200108093450607]

Flower 1972

Flower RJ, Vane JR. Inhibition of prostaglandin synthetase in brain explains the anti-pyretic activity of paracetamol (4-acetamidophenol). *Nature* 1972;**240**:410-1.

Frampton 2009

Frampton C, Quinlan J. Evidence for the use of non-steroidal anti-inflammatory drugs for acute pain in the post anaesthesia care unit. *Journal of Perioperative Practice* 2009;**19**(12):418-23. [PUBMED: 20225733]

Glenny 2005

Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, et al. International Stroke Trial Collaborative Group. Indirect comparisons of competing interventions. *Health Technology Assessment* 2005;**9**(26):1-134, iii-iv.

Graham 2005

Graham GG, Scott KF. Mechanism of action of paracetamol. *American Journal of Therapeutics* 2005;**12**(1):46-55. [PUBMED: 15662292]

Hawkey 1999

Hawkey CJ. Cox-2 inhibitors. *Lancet* 1999;**353**(9149):307-14. [DOI: 10.1016/S0140-6736(98)12154-2]

Hinz 2008

Hinz B, Cheremina O, Brune K. Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. *FASEB Journal* 2008;**22**(2):383-90. [DOI: 10.1096/fj.07-8506com]

Houde 1960

Houde RW, Wallenstein Sl, Rogers A. Clinical pharmacology of analgesics. 1. A method of assaying analgesic effect. *Clinical Pharmacology and Therapeutics* 1960;**1**:163-74. [PUBMED: 14403344]

Keats 1950

Keats AS, Beecher HK, Mosteller FC. Measurement of pathological pain in distinction to experimental pain. *Journal of Applied Physiology* 1950;**3**(1):35-44. [PUBMED: 14774320]

Kehlet 1998

Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. *Annals of Surgery* 2008;**248**(2):189-98. [DOI: 10.1097/SLA.0b013e31817f2c1a]

McQuay 1997

McQuay H, Moore A, Justins D. Treating acute pain in hospital. *BMJ* 1997;**314**(7093):1531-5. [DOI: 10.1136/bmj.314.7093.1531]

McQuay 2005

McQuay HJ, Moore RA. Placebo. *Postgraduate Medical Journal* 2005;**81**:155-60. [DOI: 10.1136/pgmj.2004.024737]

McQuay 2006

McQuay HJ, Moore A. Methods of therapeutic trials. In: McMahon SB, Koltzenburg M editor(s). Textbook of Pain. 5. Churchill Livingstone, 2006:415-26.

McQuay 2007

McQuay HJ, Moore RA. Dose-response in direct comparisons of different doses of aspirin, ibuprofen and paracetamol (acetaminophen) in analgesic studies. *British Journal of Clinical Pharmacology* 2007;**63**(3):271-8. [DOI: 10.1111/j.1365-2125.2006.02723.x]

McQuay 2012

McQuay HJ, Derry S, Eccleston C, Wiffen PJ, Moore RA. Evidence for analgesic effect in acute pain - 50 years on. *Pain* 2012;**153**(7):1364-7. [DOI: 10.1016/j.pain.2012.01.024]

Mhuircheartaigh 2009

Mhuircheartaigh RJ, Moore RA, McQuay HJ. Analysis of individual patient data from clinical trials: epidural morphine for postoperative pain. *British Journal of Anaesthesia* 2009;**103**(6):871-81. [DOI: 10.1093/bja/aep300]

Moore 1996

Moore A, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics. *Pain* 1996;**66**:229-37. [DOI: 10.1016/0304-3959(96)03032-1]

Moore 1997a

Moore A, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics: verification from independent data. *Pain* 1997;**69**:127-30. [DOI: 10.1016/S0304-3959(96)03251-4]

Moore 1997b

Moore A, Moore O, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics: use of pain intensity and visual analogue scales. *Pain* 1997;**69**:311-15. [DOI: 10.1016/S0304-3959(96)03306-4]

Moore 1997c

Moore RA, McQuay HJ. Single-patient data meta-analysis of 3453 postoperative patients: oral tramadol versus placebo, codeine and combination analgesics. *Pain* 1997;**69**:287-94. [DOI: 10.1016/S0304-3959(96)03291-5]

Moore 1998

Moore RA, Gavaghan D, Tramer MR, Collins SL, McQuay HJ. Size is everything large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. *Pain* 1998;**78**:209-16. [DOI: 10.1016/S0304-3959(98)00140-7]

Moore 2003

Moore RA, Edwards J, Barden J, McQuay HJ. Bandolier's Little Book of Pain. Oxford: Oxford University Press, 2003. [DOI: 0-19-263247-7]

Moore 2005

Moore RA, Edwards JE, McQuay HJ. Acute pain: individual patient meta-analysis shows the impact of different ways of analysing and presenting results. *Pain* 2005;**116**(3):322-31. [DOI: 10.1016/j.pain.2005.05.001]

Moore 2006

Moore A, McQuay H. Bandolier's Little Book of Making Sense of the Medical Evidence. Oxford: Oxford University Press, 2006. [ISBN: 0-19-856604-2]

Moore 2008

Moore RA, Barden J, Derry S, McQuay HJ. Managing potential publication bias. In: McQuay HJ, Kalso E, Moore RA editor(s). Systematic Reviews in Pain Research: Methodology Refined. Seattle: IASP Press, 2008:15-23. [ISBN: 978-0-931092-69-5]

Moore 2011b

Moore RA, Straube S, Paine J, Derry S, McQuay HJ. Minimum efficacy criteria for comparisons between treatments using individual patient meta-analysis of acute pain trials: examples of etoricoxib, paracetamol, ibuprofen, and ibuprofen/paracetamol combinations after third molar extraction. *Pain* 2011;**152**(5):982-9. [DOI: 10.1016/j.pain.2010.11.030]

Moore 2013

Moore RA, Straube S, Aldington D. Pain measures and cut-offs - 'no worse than mild pain' as a simple, universal outcome. *Anaesthesia* 2013;**68**(4):400-12. [DOI: 10.1111/anae.12148]

Moore 2014

Moore RA, Derry S, Straube S, Ireson-Paine J, Wiffen PJ. Faster, higher, stronger? Evidence for formulation and efficacy for ibuprofen in acute pain. *Pain* 2014;**155**(1):14-21. [DOI: 10.1016/j.pain.2013.08.013]

Moore 2015a

Moore RA, Derry S, Straube S, Ireson-Paine J, Wiffen PJ. Validating speed of onset as a key component of good analgesic response in acute pain. *European Journal of Pain* 2015;**19**(2):187-92. [DOI: 10.1002/ejp.536]

Moore 2015b

Moore RA, Derry S, Wiffen PJ, Staube S. Effects of food on pharmacokinetics of immediate release oral formulations of aspirin, dipyrone, paracetamol, and NSAIDs – systematic review. *British Journal of Clinical Pharmacology* 2015;**80**(3):381-8. [DOI: 10.1111/bcp.12628]

Moore 2015c

Moore RA, Derry S, Wiffen PJ, Straube S, Aldington DJ. Overview review: comparative efficacy of oral ibuprofen and paracetamol (acetaminophen) across acute and chronic pain conditions. *European Journal of Pain* 2015;**in press**. [DOI: 10.1002/ejp.649]

Moore 2015d

Moore RA, Derry S, Aldington D, Wiffen PJ. Adverse events associated with single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. *Cochrane Database of Systematic Reviews* 2015, Issue 10. [DOI: 10.1002/14651858.CD011407.pub2]

Pasternak 2012

Pasternak GW. Preclinical pharmacology and opioid combinations. *Pain Medicine* 2012;**13 Suppl 1**:S4-11. [DOI: 10.1111/j.1526-4637.2012.01335.x]

PIC 2008

Paracetamol Information Centre. www2.pharmweb.net/pwmirror/pwy/paracetamol/pharmwebpic.html (accessed 21 May 2015).

Salanti 2008

Salanti G, Higgins JP, Ades AE, Ioannidis JP. Evaluation of networks of randomized trials. *Statistical Methods in Medical Research* 2008;**17**(3):279-301. [DOI: 10.1177/0962280207080643]

Schwab 2003

Schwab JM, Schluesener HJ, Laufer S. COX-3: just another COX or the solitary elusive target of paracetamol?. *Lancet* 2003;**361**:981-2. [DOI: 10.1016/S0140-6736(03)12841-3]

Shea 2007

Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology* 2007;**7**:10. [DOI: 10.1186/1471-2288-7-10]

Song 2003

Song F, Altman DG, Glenny AM, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. *BMJ* 2003;**326**(7387):472. [DOI: 10.1136/bmj.326.7387.472]

Thornton 2000

Thornton A, Lee P. Publication bias in meta-analysis: its causes and consequences. *Journal of Clinical Epidemiology* 2000;**53**(2):207-16. [DOI: 10.1016/S0895-4356(99)00161-4]

Tramer 1998

Tramèr MR, Williams JE, Carroll D, Wiffen PJ, Moore RA, McQuay HJ. Comparing analgesic efficacy of non-steroidal anti-inflammatory drugs given by different routes in acute and chronic pain: a qualitative systematic review. *Acta Anaesthesiologica Scandinavica* 1998;**42**(1):71-9. [PUBMED: 9527748]

WHO 2010

World Health Organization. Pain ladder. www.who.int/cancer/palliative/painladder/en/ (accessed 21 May 2015).

References to other published versions of this review

Moore 2011a

Moore RA, Derry S, McQuay HJ, Wiffen PJ. Single dose oral analgesics for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2011, Issue 9. [DOI: 10.1002/14651858.CD008659.pub2]

ADDITIONAL TABLES

Table 1. Characteristics of included reviews. All studies included adults with at least moderate pain, and compared analgesics at various doses with placebo

Review	Date assessed as up to date	Outcomes for which data were reported	Review limitations
Aceclofenac 2009	2009	TOTPAR, SPID, remedication time, AE	None
Acemetacin 2009	2009	None	No studies found
Aspirin 2012	2011 (update in progress)	TOTPAR, SPID, remedication time, AE	None
Celecoxib 2013	October 2013	TOTPAR, SPID, remedication time, AE	None
Codeine 2010	2010	TOTPAR, SPID, remedication time, AE	None
Dexibuprofen 2009	2009	TOTPAR, SPID, remedication time, AE	Limited numbers
Diclofenac 2015	February 2015	TOTPAR, SPID,	None

Table 1. Characteristics of included reviews. All studies included adults with at least moderate pain, and compared analgesics at various doses with placebo *(Continued)*

		remedication time, AE	
Diflunisal 2010	2010	TOTPAR, SPID, remedication time, AE	None
Dihydrocodeine 2000	2011 (additional searches)	TOTPAR, SPID, remedication time, AE	None
Dipyrone 2010	2010	TOTPAR, SPID, remedication time, AE	None
Etodolac 2009	2009	TOTPAR, SPID, remedication time, AE	None
Etoricoxib 2014	2009	TOTPAR, SPID, remedication time, AE	None
Fenbufen 2009	2009	TOTPAR, SPID, remedication time, AE	None
Fenoprofen 2011	2011	TOTPAR, SPID, remedication time, AE	Limited numbers
Flurbiprofen 2009	2009	TOTPAR, SPID, remedication time, AE	None
Gabapentin 2010	2010	TOTPAR, SPID, remedication time, AE	None
Ibuprofen 2009	2009, but with additional analyses based on this review (Moore 2014)	TOTPAR, SPID, remedication time, AE	None
Ibuprofen + caffeine 2015	February 2015	TOTPAR, SPID, remedication time, AE	None
Ibuprofen + codeine 2015	December 2014	TOTPAR, SPID, remedication time, AE	None
Ibuprofen + oxycodone 2013	May 2013	TOTPAR, SPID, remedication time, AE	None
Ibuprofen + paracetamol 2013	May 2013	TOTPAR, SPID, remedication time, AE	None

Table 1. Characteristics of included reviews. All studies included adults with at least moderate pain, and compared analgesics at various doses with placebo *(Continued)*

Indometacin 2004	2011 (additional searches)	TOTPAR, SPID, remedication time, AE	Limited numbers
Ketoprofen and dexketoprofen 2009	2009	TOTPAR, SPID, remedication time, AE	None
Lornoxicam 2009	2009	TOTPAR, SPID, remedication time, AE	None
Lumiracoxib 2010	2010	TOTPAR, SPID, remedication time, AE	None
Mefenamic acid 2011	2011	TOTPAR, SPID, remedication time, AE	None
Meloxicam 2009	2009	None	No studies found
Nabumetone 2009	2009	None	No studies found
Naproxen 2009	2009	TOTPAR, SPID, remedication time, AE	None
Nefopam 2009	2009	None	No studies found
Paracetamol 2008	2008	TOTPAR, SPID, remedication time, AE	None
Paracetamol + codeine 2009	2009	TOTPAR, SPID, remedication time, AE	None
Paracetamol ± dextropropoxyphene 1999	2011 (additional searches)	TOTPAR, SPID, remedication time, AE	None
Paracetamol ± oxycodone 2009	2009	TOTPAR, SPID, remedication time, AE	None
Piroxicam 2000	2011 (additional searches)	TOTPAR, SPID, remedication time, AE	None
Rofecoxib 2009	2009	TOTPAR, SPID, remedication time, AE	None

Table 1. Characteristics of included reviews. All studies included adults with at least moderate pain, and compared analgesics at various doses with placebo *(Continued)*

Sulindac 2009	2009	None	No studies found
Tenoxicam 2009	2009	None	No studies found
Tiaprofenic acid 2009	2009	None	No studies found

AE: adverse event; SPID: summed pain intensity difference; TOTPAR: total pain relief.

APPENDICES

Appendix 1. Search strategy for Cochrane Library

1. (postoperative or (post NEXT operative)):ti,ab,kw (63669)
2. (pain or painful or analgesi*):ti,ab,kw (91468)
3. 1 and 2 (23371)
4. Limit 3 to Cochrane Reviews (231)

Appendix 2. Remedication information in individual reviews

(Continued)

Drug and dose	Mean or median time to remedication (hours)		Percentage remedicating within 6 hours		Percentage remedicating within 8 hours	
	Active	Placebo	Active	Placebo	Active	Placebo
Aspirin 600/650 mg	-	-	-	-	55	75
Aspirin 1000 mg	-	-	-		67	83
Celecoxib 200 mg	6.6	2.6	-	-	-	-
Celecoxib 400 mg	8.4	1.6	-	-	-	-
Codeine 60 mg	2.7	2	38	46	-	-
Dexketoprofen 10/12.5 mg	-	-	54	74	-	-
Dexketoprofen 20/25 mg	-	-	52	75	-	-
Diclofenac fast acting 50 mg	7.6	3.8	-	-	33	71
Diclofenac fast acting 100 mg	-	-	-	-	50	78
Diclofenac potassium 25 mg	3.1	1.2	-	-	51	71
Diclofenac potassium 50 mg	4.5	1.7	-	-	59	69
Diclofenac potassium 100 mg	6.3	2	-	-	34	72

(Continued)

Diclofenac sodium 50 mg	-	-	-	-	59	69
Diflunisal 500 mg	9.8	3.2	22	66	-	-
Diflunisal 1000 mg	10.9	3.2	23	75	-	-
Etoricoxib 120 mg	20	2	50	92	-	-
Flurbiprofen 25 mg	-	-	35	70	-	-
Flurbiprofen 50 mg	-	-	25	66	-	-
Flurbiprofen 100 mg	-	-	16	68	-	-
Gabapentin 250 mg	2.4	2.1	69	86	-	-
Ibuprofen acid 200 mg	4.7	2.1	67	87	-	-
Ibuprofen acid 400 mg	5.6	1.9	43	80	-	-
Ibuprofen fast acting 200 mg	-	-	43	78	-	-
Ibuprofen fast acting 400 mg	-	-	32	82	-	-
Ibuprofen + caffeine 100/100 mg	-	-	-	-	34	66
Ibuprofen + caffeine 200/100 mg	-	-	-	-	26	60
Ibuprofen + paracetamol 200/500 mg	7.6	1.7	-	-	34	79
Ibuprofen + paracetamol 400/1000 mg	8.3	1.7	-	-	25	79
Ibuprofen + oxycodone 400/5 mg	> 6	2.2	40	83	-	-
Ketoprofen 12.5 mg	-	-	80	98	-	-
Ketoprofen 25 mg	-	-	46	79	-	-
Ketoprofen 50 mg	-	-	48	81	-	-
Ketoprofen 100 mg	-	-	43	85	-	-
Lornoxicam 8 mg	4.7	1.4	-	-	-	-
Naproxen 500/550 mg	8.9	2	-	-	-	-
Oxycodone 5 mg	2.3	2.1	-	-	-	-
Paracetamol 500 mg	-	-	35	63	-	-
Paracetamol 600/650 mg	3.5	2.4	52	65	-	-
Paracetamol 975/1000 mg	3.9	1.7	53	72	-	-
Paracetamol + codeine 300/30 mg	3.9	2.9	48	57	-	-

(Continued)

Paracetamol + codeine 600-650/60 mg	4.1	2.4	59	80	-	-
Paracetamol + codeine 800-1000/60 mg	5	2.3	-	-	-	-
Paracetamol + oxycodone 325/5 mg	4.3	2	66	85	-	-
Paracetamol + oxycodone 650/10 mg	9.8	1.5	55	83	-	-
Paracetamol + oxycodone 1000/10 mg	8.7	1.1	-	-	-	-
Rofecoxib 50 mg	13.8	1.9	-	-	27	74

WHAT'S NEW

Date	Event	Description
19 February 2020	Amended	Clarification added to Declarations of interest.
11 October 2017	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 9, 2010
Review first published: Issue 9, 2011

Date	Event	Description
28 May 2019	Amended	Contact details updated.
14 October 2015	Amended	Reference to separate overview on adverse events updated.
28 September 2015	Review declared as stable	This review will be assessed for further updating in 2020.
4 May 2015	New search has been performed	New searches run and new reviews identified: ibuprofen + caffeine, ibuprofen + codeine, Ibuprofen + paracetamol, ibuprofen + oxycodone. New analyses for fast acting formulations for diclofenac and ibuprofen. Included reviews subject to updating include aspirin, celecoxib, diclofenac, etoricoxib, and ibuprofen (using additional data from a non-Cochrane review based on the Cochrane review of ibuprofen)
4 May 2015	New citation required and conclusions have changed	Updated review with important new review data on combination analgesics, and new analyses related to fast-acting formulations. These are typically very effective, and this changes the emphasis of the conclusions

CONTRIBUTIONS OF AUTHORS

For the original overview SD and RAM carried out searches, selected reviews for inclusion, carried out assessment of methodological quality, and extracted data. Henry McQuay and PW acted as arbitrators. All authors were involved in discussing the results and writing and approving the overview.

For this update, RAM and SD carried out searches and extracted data. All authors were involved with discussions about the review, and in writing and approving the overview.

RAM is responsible for updates.

DECLARATIONS OF INTEREST

RAM has no conflicts relating to this review or any similar product.

SD has no conflicts relating to this review or any similar product.

DA has no conflicts relating to this review or any similar product.

PJW has no conflicts relating to this review or any similar product.

We are funded by the NIHR for work on a series of reviews informing the unmet need of chronic pain and providing the evidence for treatments of pain but this review is not supported by that funding.

This review was identified in a 2019 audit as not meeting the current definition of the Cochrane Commercial Sponsorship policy. At the time of its publication it was compliant with the interpretation of the existing policy. As with all reviews, new and updated, at update this review will be revised according to 2020 policy update.

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Relief Trust, UK.

  General institutional support

External sources

- No sources of support supplied

NOTES

No updates of the included reviews are expected in the next 5 years, and no new data are likely to be available that change the conclusions for at least 10 years. This overview has now been stabilised, and will be reassessed for updating in 2027. If appropriate, we will update the overview earlier if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Pain [*drug therapy]; Administration, Oral; Analgesics [*administration & dosage] [adverse effects]; Pain, Postoperative [*drug therapy]

MeSH check words

Adult; Humans